

REMARKS/ARGUMENTS

In view of the foregoing amendments and following remarks, favorable reconsideration of the pending claims is respectfully requested.

Claim 1 has been amended by replacing the term derivative with “salt, ester, enol ether, enol ester, acid, base, solvate or hydrate” for the sole purpose of expediting prosecution. Support for this amendment is found at least on paragraph [0032] of the published application (i.e. U.S. Publication No. 2004/0209852). Claims 71 and 73 have been amended to recite ethylenediaminetetraacetic acid, citric acid, nitrilotriacetic acid, salts thereof, and sodium edentate. New independent claim 75 has been added. Claim 75 recites the combination of an antiviral agent, amphotericin β , doxycycline, and fluticasone propionate. New claim 76 has been added to recite that the antiviral agent is edoxudine. Support for these amendments is found throughout the published application. Accordingly, no new matter has been added. Claims 7-9, 16-21, 31-34 and 36-70 have been cancelled.

The Currently Claimed Invention

The currently claimed invention comprises a nasal pharmaceutical formulation for the treatment of fungus-induced rhinosinusitis comprising an aqueous suspension of a therapeutically effective amount of a drug substance, wherein the aqueous suspension has a specific suspended solid drug substance particle size distribution profile characterized by 5 different micron ratings of the solid particles of the drug substance. These formulations are suitable for intranasal administration to an individual. Accordingly, the recited particle size distributions represent solid particulates of an active drug substance (e.g. fluticasone) suspended in an aqueous medium. By utilizing solid particles of an active drug substance (e.g. fluticasone), a longer duration for treatment is achieved over formulations wherein an active drug substance is in a dissolved or liquid state. Surprisingly, formulations comprising the claimed particle size distributions provide increased bioavailability over conventional formulations when administered intranasally.

Rejections under 35 U.S.C. §112

Claims 71 and 73 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Office argues that the specification does not provide support for salts of sodium edetate. Thus, the Office concludes that the recitation of salts of sodium edetate is new matter. Claims 71 and 73 also stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite because it is unclear what is a salt of sodium edetate.

As such, Applicant has amended claims 71 and 73 to recite at least one complexing agent selected from the group consisting of ethylenediaminetetraacetic acid, citric acid, nitrilotriacetic acid, salts thereof, and sodium edetate. Applicant submits that the amendments to claim 71 and 73 overcome all rejections under 35 U.S.C. §112. Thus, Applicant requests withdrawal of the rejections based on U.S.C. §112, first paragraph, and 35 U.S.C. §112, second paragraph.

Claims 1, 3-6, 10-15, 26-28 and 30 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Office argues that “a pharmaceutically acceptable derivative of fluticasone” as recited in the claims is unclear because the application does not specifically define what is meant by the term “derivative”. The Office contends that carbon dioxide could theoretically be derived from the combustion of fluticasone as support for concluding that the skilled artisan would not be apprised of the metes and bounds of the term “derivative.” Further, the Office argues that paragraph [0032] of the present specification does not adequately define the metes and bounds of the term “derivative.”

Applicant respectfully disagrees. However, independent claim 1 has been amended by replacing the term derivative with “salt, ester, enol ether, enol ester, acid, base, solvate or hydrate” for the sole purpose of expediting prosecution. Applicant submits that the current amendment to claim 1 overcomes this rejection under 35 U.S.C. §112, second paragraph. Thus, Applicant requests withdrawal of this rejection.

Rejections under 35 U.S.C. §103

A.

Claims 1, 10-15, and 22-25 stand rejected under 35 U.S.C. §103(a) as being obvious over “FLONASE[®]” from the online Physician’s Desk Reference (“PDR[®] ”), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter “Lacy”) in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter “Bernini”).

To establish a *prima facie* case of obviousness the cited references must teach or suggest all claimed elements and there must be some suggestion or motivation to modify the references or to combine reference teachings. Additionally, a skilled artisan must have a reasonable expectation of success for modifying or combining the reference teachings.

Applicant submits the Office has not established a *prima facie* case of obviousness for at least the following reasons: (1) the cited references do not teach or suggest a nasal formulation comprising the claimed particle size distribution; (2) the necessary motivation for modifying FLONASE to contain the currently claimed particle size distribution is lacking since Bernini actually teaches away from nasal formulations as claimed; and (3) the skilled artisan would have no reasonable expectation of success for modifying FLONASE by Bernini in the manner suggested by the Office.

FLONASE is a 50 mcg of microcrystalline aqueous suspension of fluticasone propionate,. FLONASE can be used for the perennial rhinitis in patients above 12 years of age. See Lacy. As discussed in paragraphs [0053] – [0090] of Publication No. 2004/0208830 (Ser. No. 10/414,682), which was incorporated by reference in its entirety, a controlled study was performed where the fluticasone used in the Dey FP nasal spray was derived from a different source than FLONASE (i.e. the Dey FP nasal spray had a different particle size distribution than FLONASE). The Office acknowledges that Lacy does not teach the currently claimed particle size distributions, but that the particle size distribution is obviated by the teachings of Bernini.

Bernini is primarily directed to a process for preparing aqueous suspensions of drug particles for inhalation into the lungs. Bernini’s process includes the following steps: (i) preparing an aqueous solution constituting the carrier and optionally containing wetting agents,

surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients (i.e. fluticasone dipropionate); and (iv) dispersing all of the ingredients by using the sameturboemulsifier. The resulting aqueous suspensions are intended for nebulisation so that the fluticasone is deposited into the lungs.

The inhalable suspensions resulting from Bernini's process are intended for the treatment of diseases that limit airflow, such as asthma and chronic bronchitis. In particular, Bernini teaches that "[i]n order to ensure an effective penetration into the bronchioli and alveoli and hence ensure a high respirable fraction, the mean aerodynamic diameter (MMAD) of the particles should be lower than 5-6 microns. For nasal administration, particles with higher MMAD are required." See column 1, lines 33-38. As such, Bernini is silent regarding any of treating one or more symptoms of rhinitis, let alone method treating one or more symptoms of rhinitis in an individual comprising the steps of applying to the individual's nasal mucosa a single spray of a formulation having the currently claimed particle size distribution in each nostril of the individual twice daily for 9 to 14 days as currently recited in independent claim 23.

Further, Bernini teaches that the MMAD of particles should be lower than 5-6 microns to reach the lungs if administered via oral inhalation. However, Bernini teaches that if nasal administration is employed, the particle sizes having a higher MMAD are required to reach the lungs. Applicant notes that Bernini is completely silent regarding the particle size (e.g. MMAD) necessary for targeting the nasal mucosa or treating symptoms of rhinitis. Accordingly, Bernini necessarily does not provide any teaching regarding a nasal formulation suitable for intranasal administration to target the nasal mucosa.

The Office references Table 6 and Table 7 for showing particles sizes below 5 microns. However, Bernini's teachings actually provide that particles of such size are suitable for oral inhalation to reach the lungs, not intranasal administration for targeting the nasal mucosa. Moreover, Bernini's only teachings related to nasal administration specify that MMAD's above 5-6 microns are required. As such, Bernini also does not teach or suggest a nasal formulation comprising the claimed particle size distribution. In fact, Bernini teaches away from preparing

any nasal formulation having an MMAD below 5-6 microns. Consequently, the skilled artisan, in view of Bernini's teachings, would not be motivated to modify FLONASE in a manner that would result in the currently recited particle size distributions. Specifically, the necessary motivation for modifying FLONASE to have the currently claimed particle size distributions is lacking since Bernini actually teaches away from nasal formulations as claimed. As discussed above, Bernini, with respect to nasal formulations, teaches the formulations for nasal administration require an MMAD higher than 5-6.

In view of Bernini's teachings, the skilled artisan might be motivated, if at all, to manipulate the particle size distribution of FLONASE to have an MMAD above 5-6 microns. As known in the art, MMAD is the particle diameter that divides the frequency distribution in half; fifty percent of the mass has particles with a larger diameter, and fifty percent of the mass has particles with a smaller diameter. As such, Bernini is teaching that for nasal formulations, the particle size distribution should center somewhere from 5 to 6 microns. To the contrary, independent claim recites that about 50% (i.e. half) of the particles are less than 3.2 microns, while dependent claim 13 recites that about 50% (i.e. half) of the particles are less than 1.5 microns. Independent claim 35 recites that about 50% (i.e. half) of the particles are less than 2.5 microns. As such, Bernini does not provide any teaching that would lead the skilled artisan to modify any formulation, such as FLONASE, to include a distribution where 50% of the particles are less than 3.2, 2.5, or 1.5 microns as currently recited in claims 1, 35, and 13, respectively. In fact, Bernini actually teaches that distributions centered around micron ratings below 5-6 are not suitable for nasal formulations. Accordingly, the skilled artisan would not be motivated to modify FLONASE in the manner suggested by the Office.

As such, Bernini, alone or in combination with Lacy, fails teach or suggest a nasal formulation comprising the claimed particle size distribution and also fails to provide the necessary motivation for modifying FLONASE to have the currently claimed particle size distributions. As such, Applicant submits that the Office has not established a *prima facie* case of obviousness. Applicants request withdrawal of this rejection

Additionally, the skilled artisan would have no reasonable expectation of success for modifying FLONASE by Bernini in the manner suggested by the Office. Specifically, Bernini

teaches that particles with an MMAD higher than 5-6 microns are needed for nasal administration. To the contrary, the Office suggests modifying FLONASE (as shown in Lacy) to have a particle size distribution having an MMAD less than 5-6 microns. As discussed above, independent claim 1 recites that about 50% (i.e. half) of the particles are less than 3.2 microns and independent claim 35 recites that about 50% (i.e. half) of the particles are less than 2.5 microns. Since, Bernini teaches that particles with an MMAD higher than 5-6 microns are needed for nasal administration, the skilled artisan would have no reasonable expectation of success for modifying FLONASE to have an MMAD below 5-6 microns. Accordingly, the Office has not established a *prima facie* case of obviousness. Applicants request withdrawal of this rejection.

B.

Claims 3-6, 29-30 and 35 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE[®] from the online Physician's Desk Reference ("PDR[®]"), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and further in view of U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken").

The Examiner relies on Osbakken for the teaching of formulations including an antifungal agent or an antibiotic.

Osbakken is directed to compositions having a specific surface tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that "this aerosol cloud will have liquid aerosol particles" having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092].

However, Osbakken does not teach or suggest the currently claimed particle size distributions nor provide any motivation or teaching that would provide the skilled artisan a reasonable basis for modifying FLONASE to include the recited particle size distributions. As

such, Osbakken fails to cure the deficiencies of the FLONASE and Bernini. Applicant requests withdrawal of this rejection.

C.

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE[®]” from the online Physician’s Desk Reference (“PDR[®]”), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter “Doi”) and U.S. Patent No. 6,608,054 to Meade (hereinafter “Meade”).

The Office relies on Doi for teaching suspensions for nasal applications containing citric acid and EDTA. The Office cites Meade for teaching that sodium edetate and citric acid are known complexing agents.

Doi is generally directed to stabilizing an aqueous suspension of loteprednol etabonate and improving intranasal retention of the active ingredients. Doi is also concerned with the feeling-of-use using thickeners including cellulose derivatives such as methylcellulose, carboxymethylcellulose sodium, hydroxypropylmethylcellulose, etc., synthetic macromolecular compounds such as polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, etc., and saccharides such as sorbitol, mannitol, sucrose, etc.; cationic surfactants including quaternary ammonium salts; anionic surfactants including alkylsulfates; and nonionic surfactants including polysorbate 80, polyoxyethylene hydrogenated castor oil, etc.

Meade is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, neither Doi, Meade, nor any combination thereof teach or suggest the currently claimed particle size distributions nor provide any motivation or teaching that would provide the skilled artisan a reasonable basis for modifying FLONASE to include the recited particle size distributions. As such, Doi, Meade, or any combination thereof fail to cure the deficiencies of the FLONASE/Bernini or FLONASE/Bernini/Osbakken. Applicant requests withdrawal of this rejection.

Surprising Results

Further, the recited fluticasone particle size distributions provide surprising results. As Paragraphs [0053] – [0090] of Publication No. 2004/0208830 (Ser. No. 10/414,682), which was incorporated by reference in its entirety, detail a controlled study assessing the efficacy of Dey FP nasal sprays and its comparability with FLONASE. The results of which are exemplified on Figures 1-4 of the '830 publication. Of particular importance, Applicant notes that the only difference between the Dey FP nasal sprays and the FLONASE sprays was the particle size distribution of the fluticasone.

Patients who met all criteria were then randomized to 1 of 6 treatment groups:

- (1) Dey-FP 50 mcg Low Dose (100 mcg)--1 spray in each nostril daily;
- (2) Dey-FP 50 mcg High Dose (100 mcg)--1 spray in each nostril twice daily;
- (3) FLONASE Nasal Spray Low Dose (100 mcg)--1 spray in each nostril daily;
- (4) FLONASE Nasal Spray High Dose (200 mcg)--1 spray in each nostril daily twice daily;
- (5) placebo--1 spray in each nostril once daily; and
- (6) placebo--1 spray in each nostril twice daily

The patients from all six groups recorded their Total Nasal Symptom Score (TNSS) consisted of the sum of the 12-hour assessment scores for runny nose, nasal congestion, sneezing, and itchy nose recorded twice daily on the Patient's TNSS Diary card. In figures 1-4 of the present application, the efficacy of the nasal formulations is expressed as the change from baseline (pretreatment) in a composite score of nasal symptoms (e.g. runny nose, sneezing, nasal itching and congestion) referred to as total nasal symptom scores (TNSS). The change from

baseline in TNSS scores is expressed in absolute units (rather than percent change from baseline). The higher the negative value seen in the LS Mean, the greater was the change (improvement) in TNSS.

As depicted in figures 1-4 (LS MEAN as function of Days of treatment), the magnitude of improvement in TNSS for the Dey FP Low Dose group was surprisingly found to be consistently statistically superior to the FLONASE Low Dose group in relieving symptoms of SAR. Applicant notes that the FLONASE Low Dose group did realize some relief, but the magnitude of improvement in TNSS realized by the Dey FP Low Dose group was a vast improvement over the relief provided to the FLONASE Low Dose group. For example, figure 1 shows that after 1 week (7 days) of treatment, the Dey FP Low Dose group realized an LS Mean of approximately -5.9, while the FLONASE Low Dose group merely realized an LS Mean of approximately -4.5. As such, the Dey FP Low Dose group realized about a 31% improvement in TNSS over that of the FLONASE Low Dose group after 14 days of treatment. Figure 1 also shows that after 2 weeks (14 days) of treatment, the Dey FP Low Dose group realized an LS Mean of approximately -7.8, while the FLONASE Low Dose group merely realized an LS Mean of approximately -6.2. As such, the Dey FP Low Dose group realized about a 26% improvement in TNSS over that of the FLONASE Low Dose group after 14 days of treatment. Applicant submits that one skilled in the art (and one suffering from the symptoms of seasonal allergic rhinitis) would recognize that a 26% to 31% improvement due to the claimed particle size distributions is not merely a minor difference.

Even more surprising, the Dey FP Low Dose group realized better relief in TNSS than the FLONASE High Dose group. These results were surprising because the skilled artisan would not have expected the Dey FP Low Dose group to realize improved relief in TNSS over the FLONASE High Dose group, which received double the medicament. As noted above, the only difference between the Dey FP nasal sprays and the FLONASE sprays was the particle size distribution of the fluticasone.

Therefore, the fact that the claimed distributions afford unexpected results provides further evidence of the non-obviousness of the currently claimed invention.

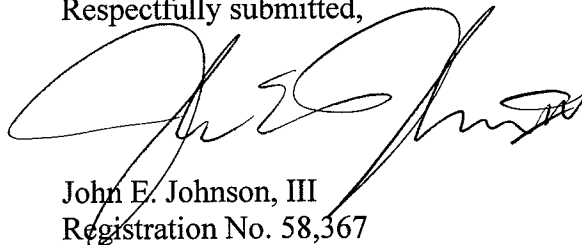
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Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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